AMENDMENT

In the Claims:

Please cancel claims 31-33 as drawn to a non-elected invention.

RESPONSE

I. Comments on Earlier Restriction Requirement

The Second Requirement at page 2 states that Applicants' earlier communication was "not fully responsive". Applicants respectfully point out that their earlier communication was as responsive as possible given the improper nature of the first Restriction Requirement.

The Second Requirement further comments that Applicants have not "provided any evidence or identify [*sic*] such evidence now of record showing that the claimed species are obvious variants or clearly admit on the record that this is the case" (Second Requirement at page 3). Applicants are unclear of the meaning intended here, particularly the reference to "species" within the section of the Requirement concerning "Groups" of invention. However, Applicants stress that no admission regarding obvious variations between any species or groups has been made and that none was intended. The initial and ongoing traversal is based on the significant procedural improprieties in the respective attempts at restriction.

II. Second Restriction Requirement

The Second Requirement now finds claims 1-38 to be drawn to three allegedly distinct inventions, set forth as:

Group I: Claims 1-11, 14-30 and 34-38, in part, said to be drawn to kits comprising at least one antibody or antigen-binding fragment thereof, a detectably-labeled antibody and a second anti-cancer agent optionally comprise [*sic*] a targeting agent and a cytotoxic agent, said to be classified in class 530, subclass 388.8+ (emphasis added);

Group II: Claims 1 and 12-13, in part, said to be drawn to kits comprising two antibody [*sic*] or antigen-binding fragments that bind to an aminophospholipids [*sic*], said to be classified in class 514, subclass 2+ (emphasis added); and

Group III: Claims 31-33, said to be drawn to an imaging kit comprising two separate pharmaceutical compositions, classified in class 424, subclass 1.11+.

III. Errors in Second Restriction Requirement

Applicants respectfully point out that the Second Requirement's characterization of claim 1 and the Group I invention is in error. The Second Requirement first states that the Group I invention is drawn to kits comprising at least one antibody or antigen-binding fragment thereof, a detectably-labeled antibody "and" a second anti-cancer agent. In contrast, the plain language of claim 1 shows the invention to be drawn to at least one antibody or antigen-binding fragment thereof that binds to an aminophospholipid in combination with either a detectably labeled antibody that binds to an aminophospholipid or at least a second anti-cancer agent.

Applicants further respectfully point out that the restriction between each of the groups in the Second Requirement is improper as it is significantly at odds with established U.S. Restriction practice, ignores proper linking claims and does not provide adequate reasoning to support restriction.

The restriction between Groups I and II is apparently based upon the reasoning that, for example, in claim 12, "utilizing a second antibody or antigen binding fragment thereof binding to a different aminophospholipid such as phosphatidylserine constitutes an additional component" (Second Requirement at page 3). This statement contains the following scientific and procedural errors showing that it is insufficient to support restriction.

First, there is nothing in claim 12 to require that the second antibody or antigen-binding fragment binds to "a different aminophospholipid". Claim 12 simply recites a first and second

antibody or antigen-binding fragment that bind to "an aminophospholipid". The target aminophospholipid could well be the same, and the antibodies or antigen-binding fragments could be different in terms of being IgG, IgM, scFv, Fv, Fab', Fab or $F(ab')_2$ fragments, monoclonal, recombinant, human, humanized, part-human chimeric, or a dimer, trimer or multimer thereof.

Second, although claim 12, for example, does require "an additional component", the requirement for restriction is not whether "an additional component" is present, but whether the claims are "patentably distinct". In this case, it is agreed that claim 1 and the Group I invention is based on the requirement for "at least one" antibody or antigen-binding fragment that binds to an aminophospholipid (Second Requirement at page 3). The "at least one" antibody or fragment includes those that bind to phosphatidylethanolamine (claim 2) and those that bind to phosphatidylserine (claim 3). So, the Group I invention requires at least one antibody or fragment that binds to an aminophospholipid, such as phosphatidylethanolamine or phosphatidylserine.

The Group II invention is drawn to kits comprising "two" antibodies or fragments that bind to an aminophospholipid (Second Requirement at page 3) and includes, in part, antibodies or fragments that bind to phosphatidylethanolamine and phosphatidylserine. The Second Requirement has advanced no reasoning to support the finding that a kit "comprising at least one" antibody or fragment that binds to an aminophospholipid is patentably distinct to a kit "comprising two" antibodies or fragments that bind to an aminophospholipid. In fact, the very language "comprising at least a first" antibody in claim 1 clearly includes the "first and second" antibodies of claims 12 and 13. The characterization of kits comprising "two" such antibodies as a patentably distinct invention is therefore improper.

The Second Requirement continues to allege that the inventions of Groups I and II are related as combination and subcombination and are distinct because "in the case of Group II, the subcombination contains materially and structurally different components. Thus, their end products are materially distinct from Group I kits, and can separately be utilized for treatment of various tumors by themselves" (Second Requirement at page 4). This statement again contains a number of scientific and procedural errors showing it to be insufficient to support restriction.

As stated above, the two antibodies or fragments in the Group II invention may not contain materially and structurally different antigen binding regions. Even if a kit of the Group II invention does contain two materially and structurally different antibodies, such that they bind to different aminophospholipids, the presence of "materially and structurally different components" is not synonymous with being "patentably distinct", such that restriction would be proper. The Second Requirement has again failed to show why a kit comprising "two" antibodies that bind to an aminophospholipid would be patentably distinct from a kit comprising "at least one" antibody that binds to an aminophospholipid.

Moreover, the comment that the Group II kits are distinct from the Group I kits as they "can separately be utilized for treatment of various tumors by themselves" (Second Requirement at page 4) does nothing to support restriction. Although the administration of two antibodies may well have certain advantages over the administration of one antibody, this is not the issue at hand. MPEP 806.05(c) clearly states "in order to establish that combination and subcombination inventions are distinct, two-way distinctness must be demonstrated. MPEP 806.05(c) at page 800-34, emphasis added. Clearly, "two" antibodies cannot be administered without administering "at least one" antibody. Therefore, two-way distinctness cannot be established and restriction is improper.

Applicants find the restriction of claims 31-33 into the Group III invention to be mysterious, as claim 1 of the Group I invention recites, in the alternative, detectably-labeled antibodies or fragments that bind to an aminophospholipid. Nonetheless, as the Second Requirement clearly includes each of claims 15-18 and 30 in the Group I invention, for the sake of efficiency, Applicants choose not to comment extensively on the diagnostic issues.

It will be noted, however, that restriction based upon combination and subcombination inventions requires two-way distinctness, which the Second Requirement fails to demonstrate. MPEP 806.05(c). In this regard, it is significant that the claimed invention as a whole does not include any claims directed solely to imaging; all imaging embodiments are claimed in terms of combined "imaging and treatment kits" (*e.g.*, claim 31). Clearly, "imaging and treatment" cannot be obtained in the absence of "treatment". Accordingly, two-way distinctness cannot be established and restriction is improper.

IV. Election with Traverse

Applicants hereby elect Group I for initial prosecution on the merits. This election is made without traverse as to the restriction between Groups I and III, but with traverse as to the restriction between Groups I and II.

V. Linking Claims

Applicants maintain that the claims of new Groups I, II and III, and particularly, the claims of new Groups I and II, should still be maintained in the case on the grounds that claims 1, 30, 33, 36 and 38, at least, are proper linking claims. The Second Requirement does not address the issue of linking claims. MPEP 809 clearly states that, even with distinct inventions, "the linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn." Any claims to

non-elected inventions, even if previously canceled, must then be reinstated in the case. MPEP 809. Applicants reserve the right to further challenge the separation of claims from the non-elected inventions upon allowance of one or more linking claims.

VI. Species Election Requirement and Response

The Second Requirement also finds the claims of all Groups to be directed to various patentably distinct species, which are set forth at pages 5 and 6. Although the species within the Group I invention appear to be somewhat confused, Applicants make the following good faith attempt at a complete election[1].

Applicants first elect "a second anti-cancer agent" (species II and VI). It is respectfully pointed out that the components apparently set forth as species II, III and IV are not, in fact, further species, but sub-species of anti-cancer agents. Applicants elect the sub-species of "apoptosis-inducing agents" as the second anti-cancer agent.

Applicants further elect monoclonal antibodies or fragments that bind to phosphatidylserine as the various sub-species of antibodies or fragments required for species I. As pointed out in response to the First Restriction Requirement, the present specification teaches the invention to include cross-reactive anti-aminophospholipid antibodies, which bind to both phosphatidylethanolamine and phosphatidylserine. Such antibodies are included within the elected species. It will also be appreciated that the election of monoclonal antibodies or fragments in no way excludes recombinant, human, humanized or chimeric antibodies or multimers thereof, as monoclonal versions of all such antibodies can readily be prepared in light of the present disclosure.

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[1] Applicants point out that the Second Requirement includes two sets of species labeled "species III", which is corrected in the Applicants' discussion.

Although not believed to be necessary, in order to avoid further procedural delays, Applicants take the precaution of electing a nuclear magnetic spin-resonance isotope as a sub-species of diagnostic agent.

Any species elections that do not contradict Applicants' earlier reasoning are made without traverse.

VII. All Species are Taught in the Specification

The Second Requirement at page 6 advises the Applicants to "select such species taught in the specification". Applicants respectfully point out that all claimed species, as well as a wide range of species not specifically recited in the claims, are taught in the specification and that the entire range of the invention as claimed could be practiced by one of ordinary skill in the art without undue experimentation in light of the present disclosure.

VIII. Status of the Claims

Claims 31-33 have been canceled as drawn to a non-elected invention, despite the presence of linking claims and without prejudice to the reinstatement of the canceled claims into the present case upon allowance of one or more linking claims. No claims have been added or amended.

Claims 1-30 and 34-38 remain pending as drawn to a unified invention, as set forth above. For the convenience of the Examiner, a copy of the pending claims is attached hereto as **Exhibit A**.

In terms of the species election, Applicants have elected a second anti-cancer agent, such as an apoptosis-inducing agent, monoclonal antibodies or fragments that at least bind to phosphatidylserine and nuclear magnetic spin-resonance isotopes. In light of the "comprising" language of the independent claims, none of the pending claims exclude kits comprising second

anti-cancer agents, such as apoptosis-inducing agents, monoclonal antibodies or fragments, antibodies or fragments that at least bind to phosphatidylserine, or the combined use of nuclear magnetic spin-resonance isotopes. Accordingly, each of claims 1-30 and 34-38 read on the elected species.

IX. Conclusion

No fees should be due in connection with the present paper. However, should any fees be deemed necessary, the Examiner is respectfully requested to telephone Applicants' representative to discuss deduction from the representatives' Deposit Account No. 50-0786/4001.002282.

This is a complete response to the referenced Requirement. In conclusion, Applicants submit that the present claims define a unified invention and respectfully request examination thereof. Should Examiner Sharareh have any questions or comments, a telephone call to the undersigned Applicant's representative is earnestly solicited.

Respectfully submitted,

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EXHIBIT A
PENDING CLAIMS
U.S. Serial No. 09/351,862 (4001.002282; UTSD:549--1)

1. A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid and:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) at least a second anti-cancer agent.

2. The kit of claim 1, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine.

3. The kit of claim 1, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine.

4. The kit of claim 1, wherein said kit comprises at least a first IgG or IgM antibody that binds to an aminophospholipid.

5. The kit of claim 1, wherein said kit comprises at least a first scFv, Fv, Fab', Fab or $F(ab')_2$ antigen-binding fragment of an antibody that binds to an aminophospholipid.

6. The kit of claim 1, wherein said kit comprises at least a first monoclonal antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

7. The kit of claim 1, wherein said kit comprises at least a first recombinant antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

8. The kit of claim 1, wherein said kit comprises at least a first human, humanized or part-human chimeric antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

9. The kit of claim 8, wherein said kit comprises at least a first antibody comprising a mouse antibody variable region that binds to an aminophospholipid operatively attached to a human antibody framework or constant region.

10. The kit of claim 8, wherein said kit comprises at least a first recombinant, human antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

11. The kit of claim 1, wherein said kit comprises at least a first dimer, trimer or multimer of an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

12. The kit of claim 1, wherein said kit comprises at least a first and second antibody, or antigen-binding fragments thereof, that bind to an aminophospholipid.

13. The kit of claim 12, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, that binds to phosphatidylethanolamine and at least a second antibody, or antigen-binding fragment thereof, that binds to phosphatidylserine.

14. The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable formulation suitable for intravenous administration.

15. The kit of claim 1, wherein said kit comprises, in distinct pharmaceutical compositions, said at least a first antibody, or antigen-binding fragment thereof, and said detectably-labeled antibody, or antigen-binding fragment thereof.

16. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the X-ray detectable compound bismuth (III), gold (III), lanthanum (III) or lead (II).

17. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the detectable radioactive ion copper^{67}, gallium^{67}, gallium^{68}, indium^{111}, indium^{113}, iodine^{123}, iodine^{125}, iodine^{131}, mercury^{197}, mercury^{203}, rhenium^{186}, rhenium^{188}, rubidium^{97}, rubidium^{103}, technetium^{99m} or yttrium^{90}.

18. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the detectable nuclear magnetic spin-resonance isotope cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III).

19. The kit of claim 1, wherein said kit comprises said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent.

20. The kit of claim 19, wherein said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent are comprised within a single pharmaceutical composition.

21. The kit of claim 19, wherein said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent are comprised within distinct pharmaceutical compositions.

22. The kit of claim 19, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent or apoptosis-inducing agent.

23. The kit of claim 19, wherein said at least a second anti-cancer agent is an antibody-therapeutic agent construct comprising a targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature; wherein said targeting antibody or fragment thereof is operatively linked to a therapeutic agent.

24. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

25. The kit of claim 24, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed component of intratumoral vasculature selected from the group consisting of an aminophospholipid, endoglin, a TGFβ receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, $\alpha_v\beta_3$ integrin, pleiotropin, endosialin and an MHC Class II protein.

26. The kit of claim 24, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-localized component of intratumoral vasculature selected from the group consisting of VEGF/VPF, FGF, TGFβ, a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF and TIMP.

27. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a cytotoxic agent.

28. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a coagulation factor or to an antibody, or antigen-binding fragment thereof, that binds to a coagulation factor.

29. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to deglycosylated ricin A chain, Tissue Factor, truncated Tissue Factor or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor or truncated Tissue Factor.

30. The kit of claim 1, wherein said kit comprises biologically effective amounts of:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) at least a second anti-cancer agent.

34. A therapeutic kit comprising, in at least a first suitable container, a combined pharmaceutically effective amount of at least a first unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; and at least a second anti-cancer agent.

35. The kit of claim 34, wherein said at least a second anti-cancer agent is an anti-angiogenic agent, apoptosis-inducing agent or a vascular targeting agent.

36. The kit of claim 34, wherein said kit further comprises a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

37. A medicinal cocktail comprising, in a pharmaceutically acceptable form, a combined effective amount of at least a first anti-cancer agent and at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

38. In combination, biologically effective amounts of:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) at least a second anti-cancer agent.